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ORIGINAL ARTICLE

Past, Present, and Future of Informed Consent in Pain and Genomics Research: Challenges Facing Global Medical Community

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■ **Abstract:** In recent decades, there has been a revision of the role of institutional review boards with the intention of protecting human subjects from harm and exploitation in research. Informed consent aims to protect the subject by explaining all of the benefits and risks associated with a specific research project. To date, there has not been a review

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published analyzing issues of informed consent in research in the field of genetic/Omics in subjects with chronic pain, and the current review aims to fill that gap in the ethical aspects of such investigation. Despite the extensive discussion on ethical challenges unique to the field of genetic/Omics, this is the first attempt at addressing ethical challenges regarding Informed Consent Forms for pain research as the primary focus. We see this contribution as an important one, for while ethical issues are too often ignored in pain research in general, the numerous arising ethical issues that are unique to pain genetic/Omics suggest that researchers in the field need to pay even greater attention to the rights of subjects/patients. This article presents the work of the Ethic Committee of the Pain-Omics Group (www.painomics.eu), a consortium of 11 centers that is running the Pain-Omics project funded by the European Community in the 7th Framework Program theme (HEALTH.2013.2.2.1-5—Understanding and controlling pain). The Ethic Committee is composed of 1 member of each group of the consortium as well as key opinion leaders in the field of ethics and pain more generally. ■

Key Words: Pain-Omics, informed consent, biobanking, standardization, privacy, protected health information, ethics committee, human biological materials

THE NEED FOR INFORMED CONSENT

The primary purpose of informed consent is to provide potential subjects with the occasion to make unbiased decisions based on the questions raised by the subject as well as the information provided by the study personnel on whether or not to take part (or to continue to participate) in a clinical research study. Every informed consent can only be valid when 2 key conditions are satisfied: (1) the information provided to the subject and (2) the consent of the subject.¹ There is a robust body of literature specifying the limitations of informed consent to obtain these targets.^{2–6} A vital point is the question of how much information is essential for the patient to be considered “informed” and whether this information can affect the results of the study, especially in patients with chronic pain for whom a placebo effect could be of great importance. Baroness O’Neill alleged that different rituals or procedures of consent should be used according to the level of risk.⁷ Therefore, one may argue that provisional language contained within the Omics research protocol is robust enough to meet or exceed the definition of “minimal risk” and may seek a waiver of consent from the appropriate institutional review board (IRB). A risk can be considered minimal when it puts subjects at levels of risk no greater than those experienced in everyday life. In this context, the risks of Omics may be low (a simple sample of human biological materials [HBMs]) or high (associated genetics maps of society and unpredictable scenarios). The risk for identification becomes progressively greater as subjects provide data via the Internet, such as names, addresses, and genetic information voluntarily and independent of research.⁸ Furthermore, not all subjects want to be informed of all of the details of specific risks, while others require a deeper understanding.⁹ Going into greater depth, what is the meaning of “understanding”? We agree with the opinion of Kettle that both clinical experience and empirical data confirm that patients’ understanding of data regarding “diagnoses, procedures, risks, and prognoses” diverge widely.¹⁰

INFORMED CONSENT AND BIOBANKING

There is a need for a clear definition of what constitutes essential information as a part of informed consent in a

research study where tissue samples and genetic materials can be stored and used at later dates, such as in Omics research. It is important to emphasize the confidentiality of all information (and how it will be addressed) as an aspect of genuine informed consent. Furthermore, the commercialization possibilities of the results, how participation in such research studies can affect a subject’s ability to be insured, and whether or not the outcomes of the research studies will be made available to the research subject are questions to which research subjects may desire answers.^{11,12} However, are those necessary concepts sufficient when we consider the vast information content involved in biobanking? Currently, large repositories of HBMs are being generated by both private and public sectors as by-products of ongoing research and for a wide variety of research uses in the future. Furthermore, those HBMs can reveal, in varying degrees, a wealth of information, such as information about the health status of the subject at the time of collection, as well as unique heritable identifiers that could lead to identification of specific individual subjects. There is a possibility that these developments could erode the effectiveness of individual or societal protections.¹³ Furthermore, these points may represent legal and ethical obstacles with the advances in global network of data sharing and use of health records for further research studies that are related to the original study, and not delineated in the original informed consent. The principal challenge is that no one can anticipate the type of information or data to be extracted from stored samples, such as biobank data in the future, or predict who or what entity can or will have access to them.¹⁴ This scenario advises for two possible options. The first option is to adapt a language that will be broad enough to cover such scenarios. The second option is to have multiple updates to the original consent form to be obtained from the subjects over time. However, both options have their drawbacks. The first option of adapting a broader language to anticipate and cover for any and all future use of the biobank data is viewed as too vague to be considered,¹⁵ although it may be considered a good compromise when managed adequately.¹⁶ The second option of continuous updates over the life of the samples in the biobank represents challenges from both practical and logistical points of view and creates a disincentive for biobank research.¹⁷

There are several ethical concerns regarding informed consent and biobanking that have been elucidated in the literature.^{13,18–20} Globally, biobanks are being set up in countries such as Canada (www.cartagene.qc.ca),

Iceland (www.decode.com), the United Kingdom (www.ukbiobank.ac.uk), and Germany (<http://national-kohorte.de>), and there are more countries who are in the process of developing similar repositories for biological samples. The biological samples stored in such biobanks are often combined with other pertinent medical or protected health information (PHI) of the individuals.²¹ These biobanks are seen as an auspicious method for providing insights into the associations between environmental factors and genetics and furthering our understanding of the causes of common diseases, thereby contributing to the development of the innovation in treatments and contributing to the development of preventative measures.¹⁴ The considerable optimism surrounding potential benefits to be gained from the research and the knowledge to be gained from the research using samples from biobanks highlights the seriousness of striking a balance between the individual concerns and the interest of society as a whole. On the other hand, there is concern that the use of biobanking may compromise privacy and confidentiality. Therefore, one significant question is how to move from a “one study/one informed consent” paradigm to something more appropriate for the extensive potential impact of biobanking on society.^{13,16,21,22} Individual consent clearly needs to be revised to take societal level interests into consideration.

STANDARDIZATION OF INFORMED CONSENT

In the field of chronic pain, biobanks could be quite useful in improving the quality and availability of large populations for studying pain syndromes, for which large population enrollment is often challenging. An additional topic of great importance is how to characterize the phenotype of pain and how to describe it to the subject in the provision of informed consent. In most genetic/Omic trials, it is not sufficient^{23,24} to consider efficacy based merely on “a number” as assessed by a numeric rating scale or visual analog scale. Rather, it is crucial to more broadly capture the outcome experience of subjects with chronic pain²⁵ by assessing other outcome dimensions (eg, emotional status, functionality). Furthermore, we should strive for a general international consensus regarding the phenotype measures of chronic pain that would be relevant to correlate with genetic/Omic data. Such a widespread consensus would serve to improve the results of genetic/Omic studies of pain and additionally will make the process of informed consent more objective and standardized. For example, the Pain-Omics group

has adopted a minimal common dataset of clinical features on all of its genetic/Omic studies that clarifies informed consent for subjects.

Another salient concern is related to the use of anonymous data. In the past decades, the concept that the use of coded information could not result in any harm to the individual was frankly inaccurate.⁸ According to this notion, no informed consent is needed if the biological samples used for research do not contain any personal identifiers to prevent identification of the subject who provided them.²⁶ In fact, there are greater than 307 million human biological materials being stored in the United States, and most of them were obtained without informed consent for research.²⁷ Some countries accept the waived consent for some research. Examples of such are Canada, based upon its Personal Information Protection and Electronic Documents Act (PIPEDA),²⁸ or the United States according to the federal regulations under 45 CFR 46.116, known as common rules summary conditions under which data may be used for research purposes without individual consent.²⁹ In other countries, it is almost impossible to use data and samples taken without written consent for research purposes outside the institution in which they were taken. For example, in Germany, the Federal Data Protection Act prohibits use of data (and thus data generated from biomaterial) without permission of the donor or a legal representative.

Furthermore, recent studies have demonstrated the ease of deducing specific identity from different public datasets. For example, in one study,⁸ the researchers were able to find the identity of nearly 50 participants through publically available information. Such results point to the fact of how easily data are accessible in the networks. Therefore, specific consideration should be paid to protect and preserve the privacy rights of research participants in this new era of information technology.³⁰ The suggestion of the authors is to limit access to the minimum staff necessary to perform the primary study, ensuring appropriate dissemination of the results. The use of anonymous/pseudonymous data is mandatory. Research institutions in some nations attempt to reduce the impact of this problem by informing the subject about the possibility of public identification when genetic information is online.

OPTIONS FOR INFORMED CONSENT

An additional question relates to researchers' options regarding identifiable samples with associated relevant clinical information. There are multiple options:

contacting sample providers and attempting to obtain informed consent (which is likely to be challenging logistically), making samples unidentifiable (thereby limiting the empirical value of the samples through deletion of the connection to the highly relevant clinical information), or seeking a waiver of consent from the IRB (minimal risk standard) if permissible. In contrast to prospective research, informed consent for Omics is no different from that pertaining to clinical trials. However, there is substantial divergence from traditional research, which pertains to the possibilities that the collection of HBMs will be stored for future undetermined use and that samples and data will be handed over to other institutions.

Thus, we suggest that informed consent forms of prospective studies consider including the following options²⁶:

- Refusing to use the HBMs for any research.
- If subject agrees to the use of HBM consider the following options
 - HBM use without PHI
 - Permitting only unidentified or unlinked use.
 - Permitting coded use for any type of future research.
 - HBM use with PHI (all or parts of it) permitted
 - Permitting coded or identified use for a particular study, with no further contact with the subject regardless of health or genetic discovery.
 - Permitting coded or identified use for a particular study, with further contact regarding new findings or to update an informed consent.
 - Permitting coded or identified use for any study relating to the condition, with further contact permitted regarding new discoveries or updates for informed consent for future use.
- For all HBM samples a set an expiration date, and after which the samples and any and all PHI will be destroyed along with HBM.
 - Verification of sample destruction will be sent to individual subjects.
 - Or a generic notification to all study subjects.

Furthermore, the standards used for traditional research should not necessarily be used for Omics research. With a provocative title (“Ethics review

roulette”),³¹ Glasziou and Chalmers concluded that ethical standards are essential for all types of evaluations, yet the concept of “one size of ethics review fits all types of evaluation” should be rejected. There is consensus that standards in Omics and biobanking ethics need to be optimized, and that multiple new approaches are developed to achieve such optimization.^{16,32–34}

Another important issue is the huge differences between the applications of the general ethical recommendations for different IRBs. Several investigators have described the differences regarding ethical requirements and submission particulars in European nations.^{35,36} In an interesting investigation, Stamer and colleagues³⁷ compared ethical procedures in a multi-center postoperative pain study. These investigators observed that the approval process can range from less than 2 weeks to more than 2 months, with participation fees varying from 300 to 575 Euros. Additionally, regarding informed consent, there were substantial differences between centers not only regarding information sheets of variable length (ranging from half a page up to 2 pages) but also the nature of what constituted informed consent. Written informed consent was mandatory at 12 centers, only oral consent was required at 10, with 1 center requiring no consent whatsoever. The need for multiple ethical approvals for multicenter studies and increasing ethical regulations and guidelines have become barriers to research,³⁸ especially in genetic/Omic pain research (in which the ethical implications associated with trial approval are even more significant).³⁵ In Europe, several ongoing projects are aimed at centralizing IRB approval. Examples of these projects include the European Clinical Research Infrastructures Network (ECRIN; <http://www.ecrin.org/>) and the European Forum for Good Clinical Practice (EFGCP; <http://www.efgcp.be/EFGCPRReports.asp>). Although the focus remains predominately on interventional trials, there remains a need to adopt procedures more specific to this type of research.

THE AMERICAN DILEMMAS AROUND INFORMED CONSENT AND PRIVACY

In the United States, the situation is similar. However, although privacy issues around pain pharmacogenomics are relatively straightforward in nations with National Health Services, in the United States, where a national healthcare system does not exist, it takes a very conservative approach when it comes to privacy issues,³⁹ which results in certain unique ethical

quandaries associated with privacy. Among the most distressing of these issues is the limitation of the Genetic Information Nondiscrimination Act (GINA) of 2008. GINA was heralded as “the first civil rights legislation of the new millennium”⁴⁰ and was met with considerable enthusiasm until the weaknesses of the legislation were better understood.⁴¹ To its credit, GINA prohibits health insurers from denying coverage to an individual for having heightened genetic risk for developing a disease—provided that the individual is asymptomatic.⁴² Unfortunately, the law does not prohibit insurers from denying coverage when applying for disability, long-term care, or life insurance.⁴³ While Rothstein⁴⁴ has argued that GINA has symbolic value in alleviating fears of discrimination and thereby allows individuals at risk to use genetic testing more freely, a recent study⁴⁵ determined that the weaknesses of the law in regard to providing privacy of results remains a concern for the majority of those who would consider such testing. Given the severity of the discrimination already experienced by those suffering from chronic pain,⁴⁶ the American government has not yet enacted legislation that adequately protects the privacy of pharmacogenomic testing for pain—resulting in tragic limitations of its empirical investigation and clinical utility.

ADDITIONAL CONCERNS

Omics research in patients with pain is a new and innovative field that has the potential to produce a wide array of novel medical treatments. The potential uses of this innovative research include identifying biomarkers for specific clinical pathologies (eg, low back pain), understanding the variation of gene expression in cytokines genes and opioid pathways in several clinical models of acute pain, and identifying single nucleotide polymorphisms (SNPs) related to individual variability of pain experience. These issues add new ethical complexity to the scenario.^{47,48} The misuse of Omics data in research indeed involves potential risks, but its inclusion in clinical practice opens the door to other risks as well. What would happen, for example, if employers were to use pain sensitivity information to exclude employees with a high risk for back pain? Or if an insurance company were to use them to avoid covering high-risk individuals? These possibilities are not necessarily as remote as one may believe, particularly given their histories in the United States. In 2001, the Burlington Northern Santa Fe Railway Company was sued by the Equal Employment Opportunity Commission, which alleged that the

company discriminated against its own employees when it performed genetic testing of their employees using blood samples obtained without individual informed consent specific for the genetic testing and without the employee’s knowledge.⁴⁹ Nonetheless, insurers’ misuse and potential abuse of information arising from Omics studies of pain is one of many hypothetical and practical ethical dilemmas potentially associated with any research studies that collect and generate genetic data.

An additional topic of ongoing concern is protection of vulnerable populations. When designing a pain research study, one must ensure that subjects are able to correctly comprehend the scope of the clinical trial, to “correctly” express pain, and to provide legitimate consent.⁵⁰ Particularly at the cognitive level, the ability to comprehend and provide consent becomes even more critical as an increasing number of pain research projects begin to utilize HBMs, specifically when subjects are asked to understand complex implications and potential misuse of information as a result of participating in a research study with HBMs. Furthermore, at a physiological level, one must be careful to prevent unnecessary pain in research subjects, either deliberately or unintentionally by design for the sake of clinical pain research. A particularly salient example pertains to cases of fetal, neonatal, and infant pain. In a famous case performed in 1985, open heart surgery was performed on a premature infant named Jeffrey Lawson while the infant was fully awake and conscious during the entire operation without any analgesic or anesthetic administered to the infant either perioperatively or intra-operatively. The anesthesiologist at the time argued that it had not ever been established that pain was experienced in premature babies.⁵¹ In considering a recent study proposal, however, an IRB rejected a research protocol using placebo to study neonatal pain in an intensive care setting.⁵² Despite such precedents in the research arena, invasive and potentially painful fetal procedures continue to be performed in clinical practice. Another important area of research is pain in elderly patients, due to the high prevalence of both pain and cognitive impairments in the elderly population. It is a well-documented fact that difficulties associated with the assessment of pain in elderly and/or cognitively impaired subjects lead to a suboptimal management of pain.^{53,54} There are several methodological obstacles in research in this field⁵⁴; for example, in the contemporary practice of clinical studies, cognitively impaired patients are excluded from research protocols. The improvement of pain monitoring in patients could be a new way to improve our

knowledge in these areas. The principal aim would be to obtain the minimum intensity of pain essential to complete the objectives of the research.⁴⁷

CONCLUSIONS

Although informed consent is widely accepted in many countries, this understanding varies according to the culture and background of the different healthcare personnel involved. Informed consent in Pain-Omics research involves more than a few particular ethical concerns, including those associated with the biobanking of HBMs and the future use of stored material for further indeterminate research. Careful efforts to clarify practice and the critical role of informed consent are necessary to bridge the gap between the current realities of informed consent and those of the desired future direction.⁵⁵ Continued persistent and thoughtful efforts to bring the theoretical and practical realities of informed consent closer together are essential. The European scientific community would benefit from developing a protocol aiming to protect human subjects from harm and exploitation and to reduce the bureaucratic burden of procedures for managing the enormous quantity of information involved in Pain-Omics. The potential future benefits to the practice of medicine and society as a whole associated with such an innovative type of approach are simply dramatic.

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APPENDIX 1

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